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# Intermediate Outcome and Risk Factor Assessment of Bovine Vascular Heterografts used as AV-Fistulas for Hemodialysis Access

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***Objectives.*** *This observational study was set up to prospectively follow all bovine heterograft (ProCol®) fistulas implanted for hemodialysis access between 1998 and 2002.*
***Methods.*** *ProCol® was implanted if autogenous vein was not available or if patients presented with a history of failed, infected or otherwise complicated ePTFE grafts and/or on immunosuppressive therapy. Fistula patency was the primary outcome; secondary outcomes were clinical events and the rate of access revisions.*
***Results.*** *Sixty-two ProCol® grafts were implanted in 56 patients. The mean primary (PP) and secondary patency (SP) was 334 (SEM 57) and 528 (SEM 59) days, respectively. Coronary heart disease was associated with a significantly better SP (OR 0.2, 95% CI 0.1–0.9) whilst diabetes mellitus was associated with a significantly worse SP (OR 0.2, 95% CI 0.1–0.9). Reinterventions were performed at a mean rate of 1.23 (SEM 0.17) per fistula. The relative risk of access revision was significantly higher in patients with diabetes mellitus (OR 9.2, 95% CI 2.3–37.2).*
***Conclusions.*** *ProCol® grafts, used for AV-fistulas, demonstrate acceptable patency rates in high-risk haemodialysis patients. Diabetes mellitus jeopardizes the patency of these fistulas and is associated with a high revision rate.*

*Key Words: Arteriovenous fistula; Hemodialysis; Xenografts; Bovine; Risk factor.*

## Introduction

Arteriovenous (AV) fistulas are the primary method of long-term hemodialysis access. Autogenous radial- or brachial-cephalic AV-fistulas are preferred types of primary hemodialysis access due to excellent patency, low complication rates and acceptable periinterventional morbidity.[1–10] If an autogenous fistula is impractical, prosthetic or biological AV-grafts provide an alternative approach.[11] They offer a large surface area, allowing simple cannulation, a short maturation period and easy surgical handling.[12–17]

Despite these advantages, reduced primary and secondary patency (PP/SP) rates, infections, and pseudoaneurysms have been more frequently reported with the commonly used polytetrafluoroethylene (PTFE) grafts.[1,7,18] Bovine heterografts have also been used in the hope that they would be more resistant to infection but their use was complicated by rupture and life-threatening haemorrhage.[19,20] Regardless of these complications, several retrospective series have found that the patency rates of these grafts are comparable to PTFE.[18,21] Current NKF-K/DOQI guidelines do not favour the use of these heterografts due to the aforementioned complications.[11] However, ProCol®, a denatured bovine vessel-based bioartificial vascular conduit has recently been introduced. Based on its high elastin to collagen ratio, less anastomotic site compliance mismatch is expected. This is thought to reduce para-anastomotic subintimal hyperplasia.[22]

Although this graft was introduced with conflicting results in infrainguinal reconstructions,[23] Bacchini *et al*. reported a series of 63 ePTFE and 22 ProCol® implants in 53 hemodialysis patients with superior PP and SP compared to bovine vein graft.[24]

The objective of this prospective, non-randomized, observational study was to demonstrate the feasibility, patency and complication rate following ProCol® grafting between October 1998 and April 2002 in a group of high-risk hemodialysis patients. Potential

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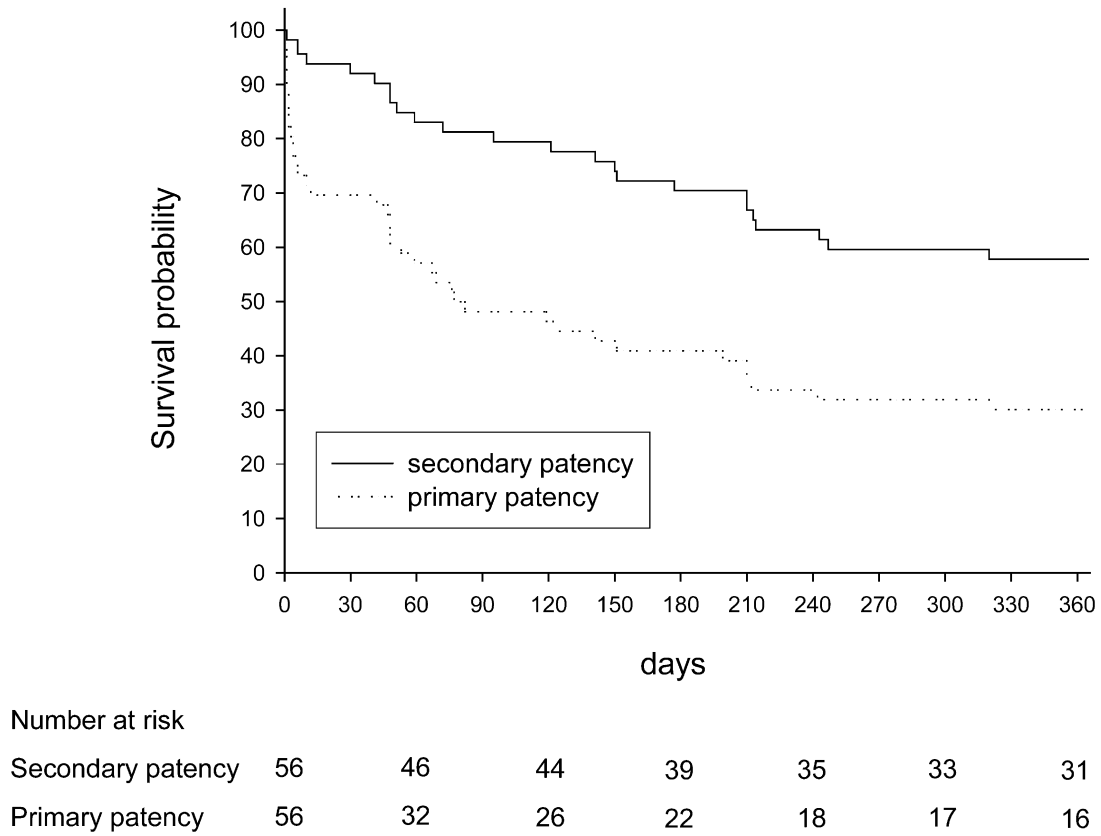


**Fig. 1.** Survival probability with primary or secondary patency.

risk factors for an adverse outcome were also evaluated.

## Materials and Methods

Between October 1998 and April 2002, 319 de novo AV-fistulas were created for haemodialysis access, of which 187 were autogenous. Sixty-two ProCol® grafts were implanted in 56 patients. Redo ProCol® grafts in six patients were excluded from the evaluation. ProCol® was used in patients with insufficient vein for autogenous fistula placement, as assessed by Doppler screening, and who had a history of failed, infected or otherwise complicated PTFE grafts, immunosuppressive therapy, or diabetic patients with infectious skin problems. The most peripheral site of the non-dominant arm with sufficient arterial inflow, and veins ($>3$ mm) was preferentially used. In 9% of the patients, peripheral steal was anticipated and the ProCol® graft diameter was restricted to 4 mm. In all other cases 6 mm implants were employed.

Under plexus anesthesia, atraumatic tunneling connected the vessel sites. Grafts were prepared by rinsing three times with sterile saline with 40 IU Na-heparinate/ml and controlled for the correct flow direction as instructed by the manufacturer. Anastomoses were performed with a monofilament running suture (Prolene® 6-0).

Baseline data on the aetiology of renal failure, risk factors and demographics, as well as the history of renal replacement therapy including prior shunt placement and informed consent were obtained before implantation. Intraoperative data were recorded as well as post-operative follow-up. Intraoperative blood flow was measured using the transit time method transmitting ultrasound created by two piezoelectric crystals transvascular towards a reflector on the opposite side of the vessel. Flow volume was calculated by measuring transit times. We used the CardioMed Flowmeter (Medi-Stim AS, Oslo, Norway) with 6 mm probe according to Beldi *et al*.[25]

Outcome parameters are detailed according to the reporting standards for vascular grafts suggested by Sidawy *et al*.[26] Patency and complication rates were calculated starting at the date of implantation to either renal transplantation, death or as defined by Sidawy *et al*.[26]

All statistical analyses were performed using SYSTAT Version 10 (SPSS Inc., Chicago, IL). ($\chi^2$ testing,

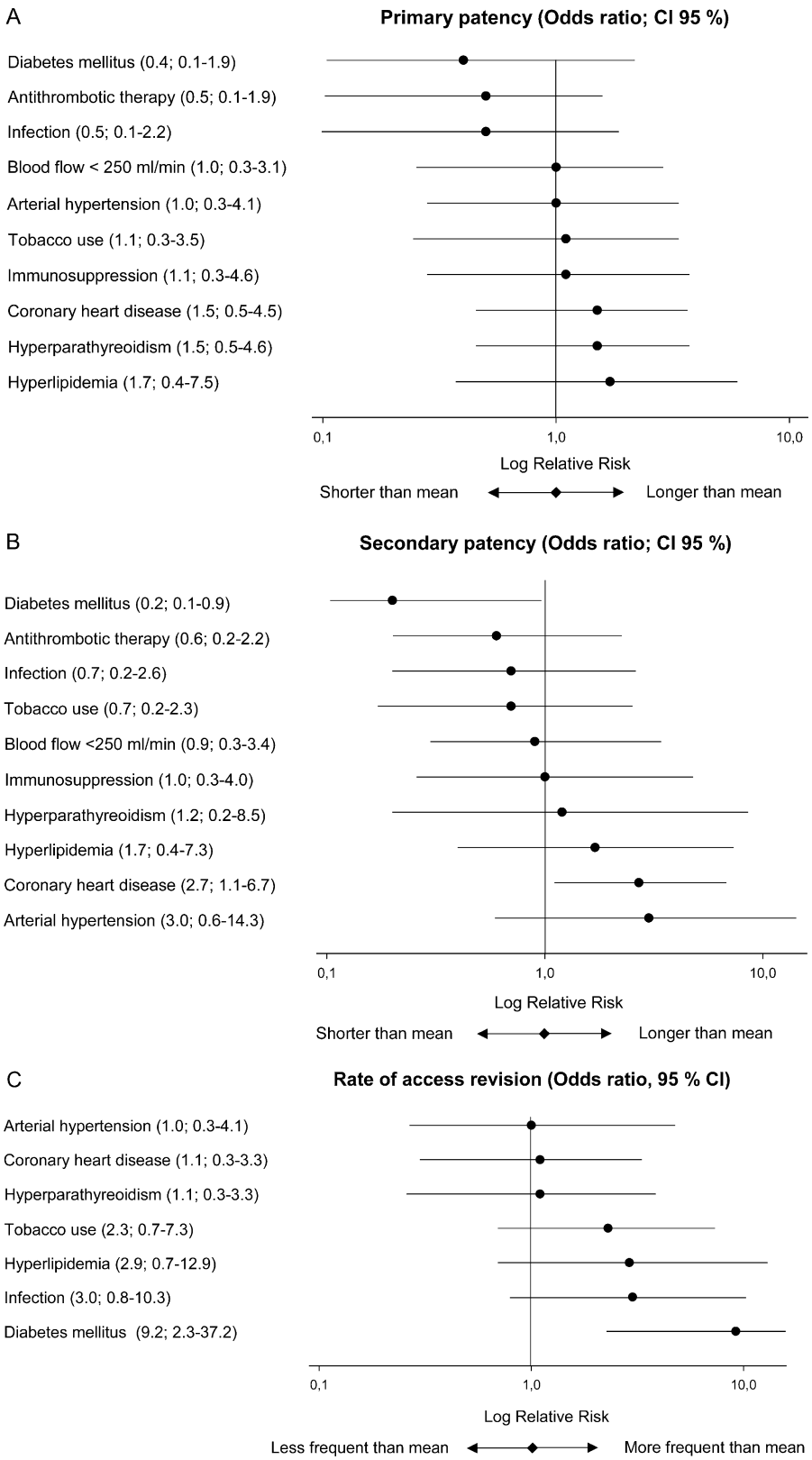


**Fig. 2.** (A) Relative risk for a less than average primary patency. Indicated are odds ratios ±95% confidence intervals. (B) Relative risk for a less than average secondary patency. Indicated are odds ratios ±95% confidence intervals. (C) Relative risk for more than average access revisions. Indicated are odds ratios ± 95% confidence intervals.

Student's *t*-test, and Cox proportional hazards regression were applied. Univariate analysis of the PP and SP of the first fistula used the Kaplan–Meier technique, with date of fistula failure as the uncensored end point. Logistic regression was used to evaluate the statistical association between PP, SP, rate of access revision and risk factors. The contribution of covariates to explain the dependent variable was assessed by means of a two-tailed likelihood ratio test, with $p < 0.05$ considered significant. All data are presented as absolute numbers, range, or mean and SEM. Estimated relative risks (OR) and their 95% confidence intervals (CI) are reported for all variables.

## Results

Sixty-two Procol® fistulas were placed. The mean age of the study population on referral was 63.5 (SEM 1.8) years and 61% were men. The majority of these patients (70%) was already on chronic intermittent hemodialysis treatment while only 21% required immediate de novo dialysis treatment, indicated by the average time on dialysis (854, SEM 213 days). In contrast, two patients with pre-emptive fistula placement did not receive dialysis treatment during the observation period as one died and one received a successful renal transplant. The most common reasons for end-stage renal failure were glomerulonephritis (18%), vascular (16%) or diabetic nephropathy (14%), vasculitis (9%) and cystic kidney disease (9%).

The follow-up ranged from 1 to 1401 days (mean 453, SEM 53). During the follow-up period, 13 patients (23%) died, four (7%) received a renal transplant and in one patient renal function recovered. The majority of grafts were placed in a forearm location (71%), preferably straight (59%) and the mean implantation time was 148 (SEM 11) min. The long procedure time was because almost all extremities used had had former placement attempts. Kaplan–Meier life table evaluation revealed a patency of 43 and 73% at 6 months and of 30 and 58% at 12 months for PP and SP, respectively (Fig. 1). No interventional radiological procedures to maintain patency were performed on these fistulas. Risk factor analysis showed only a minor increase of the calculated risk in fistulas patent $<6$ months when compared to those patent $>6$ months: (7.3, SEM 0.43 vs. 6.8, SEM 0.37 and 7.50, SEM 0.52 vs. 6.9 SEM 0.35 for PP and SP, respectively).

Several potential risk factors were evaluated for their effect on fistula patency. PP was longest in the presence of coronary heart disease independent of the use of anti-platelet drugs or oral anticoagulants although the relative risk analysis did not indicate a significant benefit or disadvantage for any analyzed factor with regard to PP (Fig. 2(A)). In contrast, with regard to SP an independent risk reduction was evident for patients with coronary heart disease (OR 0.2, 95% CI 0.1–0.9) and an independent risk progression for patients with diabetes mellitus (OR 0.2, 95% CI 0.1–0.9, Fig. 2(B)).

The mean fistula blood flow was $>400$ ml/min (435, SEM 36). A flow rate of $<250$ ml/min was observed in eight patients with only modest reduction in PP and SP[27] and flow rates did not predict patency. Antithrombotic therapy was continued in 79% of the patients at discharge using acetylsalicylic acid, warfarin or clopidogrel but there was no association with continued patency.

The mean reintervention rate was 1.23 (SEM 0.17) per fistula. At least one revision was required to maintain the patency of 70% of the fistulae and 7% needed four or more procedures. Most frequently, fistulae required revisions for thrombosis (66%) or venous stenosis (16%), less often due to other conditions such as infections (10%) or peripheral steal (8%). The relative risk of access revision was significantly higher in patients with diabetes mellitus (OR 9.2, 95% CI 2.3–37.2). Eighteen fistulae had to be explanted for various reasons, such as recurrent thrombosis (11%), stenosis (4%), steal (2%), granulomatous disease (2%), bleeding (2%), and recovered renal function (2%). Thirteen infections occurred, six (11%) required surgical excision of the fistula. There was no difference in the frequency of infections with respect to perisurgical antibiotic prophylaxis, which had been given in 50% of the cases. In two patients, a profound dilatation of the graft was observed but no intervention was required.

## Discussion

Vascular access problems remain the leading cause of morbidity in the haemodialysis population despite much interest in improving outcomes, such as the DOQI guidelines.[11] In this observational study, a high-risk population of haemodialysis patients, indicated by the high mortality rate during the follow-up period, was monitored. In the absence of suitable autologous veins, subcutaneous access placement of bioartificial material, such as ProCol®, is preferable to transcutaneous access.[11] ProCol® mimics the wall structure of human vessels, and is believed to provide enhanced resistance to infection compared to prosthetic grafts. The decision to implant a ProCol® graft was taken because autogenous veins, as mandated by the DOQI

guidelines, were absent and because the patients' history did not favour a PTFE graft.

The primary intention was the creation of a forearm fistula.[28] This strategy may have led to the requirement of additional revisions and extended implantation times, but may have saved future access sites.[29]

The patency of fistulas is determined by local and systemic conditions, but also by patient-related events. Grading of risk factors as proposed by Sidaway *et al*.[26] did not allow discrimination between fistulae with patency shorter and longer than 6 months, indicating that this high-risk population of hemodialysis patients was very homogenous. The longest primary patency rates were observed in patients with coronary heart disease, a finding that was not associated with the use of an oral antithrombotic drug. The decision to start antithrombotic therapy may have been biased by complicated fistulas or a low intrasurgical blood flow measurement, but it did not improve patency. The SP was significantly better in patients with coronary heart disease and worse in those with diabetes mellitus. As suggested by the DOPPS study, calcium channel blockers may improve PP and angiotensin converting enzyme inhibitors (ACEI) SP.[30] Calcium channel blocker, ACEI, angiotensin II receptor blocker and β-blocker are drugs given to patients with coronary heart disease in end-stage renal disease.[31] The risk reduction for cardiovascular mortality and potentially for graft failure is based on several beneficial effects, such as blood pressure control, antiproliferative properties, the reduction of the sympathetic tone or the pulse wave velocity.[32–34] Gibson *et al*.[29] described an increased risk of revision in diabetic patients, a finding in line with our own observation. The majority of revisions occurred due to early thrombosis within the graft or at the anastomotic sites similar to an earlier study comparing PVAG and ePTFE.[28] A potential explanation for this problem may be the local thrombogenicity of the graft wall due to the continuous release of glutaraldehyde.

It is of interest to compare the patency rates obtained here with those in other types of fistulas, such as ePTFE, polyurethanurea vascular access graft or further heterografts. These comparisons are often complicated by the heterogeneity of the patient groups. Comparing ePTFE with PVAG, Glickman *et al*.[28] reported higher 12-month patency rates of 78–80% but their study included less men and less patients with prior hemodialysis treatment. In contrast, SP rates in complicated transposition fistulas have been described to be even lower than in our study.[35] In a recent review of the literature, SP rate for PTFE accesses was 76% at 6 months i.e. very similar to our findings.[36]

In conclusion, these data suggest that ProCol® grafts can be used for AV-fistulas with reasonable results in high-risk patients without autogenous vein. The favorable outcome in patients with coronary heart disease deserves further evaluation to identify beneficial factors, such as co-medication. In contrast, diabetic patients have an increased risk of reduced patency and more access revisions.

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